REMARKS

Claims 1-20, 23, 26, and 31-40 have been canceled. Claims 21, 22, 24, 25, 27-30, and 41-45 are currently pending in the present Application. Claims 21, 22, 27, 28, and 43-45 are actively being prosecuted. Please note that claim 21 has been amended by the Amendment faxed to the Examiner on April 7, 2003.

Applicants are submitting herewith the Declaration of Lars Michael Furness. The Furness Declaration is being submitted as corroborating evidence of the real-world utility of the claimed invention by virtue of its use in toxicology testing, drug development and disease diagnosis through protein expression profiling. The Furness Declaration describes some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood by one of skill in the art at the time of the patent application. The Furness Declaration presents objective evidence that the utilities of toxicology testing, disease diagnosis and drug development used the well known molecular biology technique of 2-D PAGE and as such, these well known utilities and uses do not have to be asserted in the Specification.

Rejoinder of Claims

Applicants continue to request the rejoinder of claims 24, 25, 29, 30, 41 and 42 which are "method of making" and "method of use" for the polypeptides of product claim 21. Therefore, upon allowance of a product claim, it is believed that claims 24, 25, 29, 30, 41 and 42 should be rejoined and considered in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)." See also MPEP § 821.04 Rejoinder which states:

> if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claims will be rejoined.

Rejection under 35 U.S.C. §112, first paragraph, enablement

Claims 21, 27, 28 and 43-45 were rejected under 35 U.S.C. §112, first paragraph, allegedly because "the specification does not reasonably provide enablement commensurate with the scope of the claimed invention." The Office further asserts that:

- The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species (Office Action of June 17, 2003, page 3).

- Since the amino acid sequence of a protein determines its structural and functional properties, knowledge of which sequences of the amino acids would retain similar biological activity and immunogenicity the same as Applicants' is required (Office Action of June 17, 2003, page 3).

At the outset, Applicants note that claim 22 is **not** included in this rejection. Accordingly, it is submitted that the Examiner concedes that the Specification as filed does at least **enable** one skilled in the relevant art to which it pertains, or with which it is most nearly connected, to make and use the polypeptide having the sequence of SEQ ID NO:3.

Applicants travers this rejection for the reasons submitted below.

A. Legal Requirement

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

To fulfill the enablement requirement of 35 U.S.C. §112, first paragraph, the claimed invention must be described in the Specification in such as way as to enable one skilled in the relevant art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

When determining whether the Specification meets the enablement requirement the courts have ruled that the claimed invention be disclosed in the patent together with information known in the art such that one of ordinary skill in the art is *enabled* to make and use the invention without undue experimentation. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988); *United*

States v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). Thus, "a patent need not teach, and preferably omits, what is ***well known*** in the art. *In re Buchner,* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied,* 480 U&.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

In addition, the Manual of Patent Examination Procedure at § 2164.01(c) states:

> [A]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 824 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir.), *cert. denied,* 484 U.S. 954 (1987).

It is submitted that the Specification does reasonably provide an adequate written description to **enable** the claimed polypeptides of SEQ ID NO:3 and SEQ ID NO:5 as well as the recited naturally-occurring 90% variants of "the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, said polypeptide having apoptotic activity," biologically-active fragments "of a polypeptide having the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, said fragment having apoptotic activity" and immunogenic fragments of SEQ ID NO:3 or SEQ ID NO:5 (the amino acid sequences of HAPOP-2 and HAPOP-3, respectively) at the time of filing of this application.

B. Applicants have established that one skilled in the art would understand that there is a "well established" utility for the claimed invention

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through protein expression profiling. The uses of HAPOP-2 and HAPOP-3 for toxicology testing, drug discovery, and disease diagnosis are practical, ***well known*** uses that confer "specific benefits" to the public. These uses are explained in detail in the Furness Declaration, submitted herewith.

Two ***well known*** protein expression profiling techniques in molecular biology are protein microarrays and 2-D PAGE. Protein expression monitoring applications are known by the skilled artisan to be useful in connection with drug development and monitoring the activity of drugs. Further, the skilled artisan recognizes the use of 2-D PAGE mapping in the study of protein expression and its regulation in response to drugs and toxic agents. The Furness Declaration provides corroborating evidence of the well established and ***well known*** uses of 2-D PAGE in protein expression profiling:

> In addition, at the time of filing the Hillman '402 application, it was well known in the art that "gene" and protein expression analyses also included two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) technologies, which were developed during the 1980s, and as exemplified by the Anderson 1991 and 1995 articles (Tab A and Tab B). The Anderson 1991 article teaches that a 2-D PAGE map has been used to connect and compare hundreds of 2-D gels of rat liver samples from a variety of studies including regulation of protein expression by various drugs and toxic agents (Tab A at p. 907). The Anderson 1991 article teaches an empirically-determined standard curve fitted to a series of identified proteins based upon amino acid chain length (Tab A at p. 911) and how that standard curve can be used in protein expression analysis. The Anderson 1991 article teaches that "there is a long-term need for a comprehensive database of liver proteins" (Tab A at p. 912).
>
> The Wilkins article is one of a number of documents that were published prior to the May 13, 1998 filing date of the Hillman '402 application that describes the use of the 2-D PAGE technology in a wide range of gene and protein expression monitoring applications, including monitoring and analyzing protein expression patterns in human cancer, human serum plasma proteins, and in rodent liver following exposure to toxins. In view of the Hillman '402 application, the Wilkins article, and other related pre-May 13, 1998 publications, persons skilled in the art on May 13, 1998 clearly would have understood the Hillman '402 application to disclose the SEQ ID NO:3 and SEQ ID NO:5 polypeptides to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 12 below. (Furness Declaration, paragraph 10, page 8).

Accordingly, 2-D PAGE is and was a well known technique for many years prior to the filing of the parent application, May 13, 1998, and as such, one of skill in the art would recognize the use of the claimed invention in such a well known technique as applicable to the instant invention when using the claimed invention in toxicity testing, drug development and diagnosis of disease without having to specifically set forth the details of how to perform these protein expression profiling techniques. Thus, Applicants have provide enablement commensurate with the scope of the claimed invention such that

the reasonably skilled artisan is enabled to use the claimed invention in protein expression monitoring applications including toxicology testing, drug development and disease diagnosis.

C. The Furness Declaration is Submitted in Support of the "Well-Established" and/or Asserted Utilities of HAPOP-2 and HAPOP-3, and thus, at Least One Utility for SEQ ID NO:3 and SEQ ID NO:5

The Declaration of Lars Michael Furness presents objective evidence of at least one well-established utility for the claimed invention. The Furness Declaration describes some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood by one of skill in the art at the time of the patent application. These utilities are both ***well established*** and asserted in the Specification.

The Furness Declaration is submitted to corroborate Applicants' established, real world utility for the instant invention in toxicology testing, disease diagnosis and drug development. The Furness Declaration explains the many reasons why the claimed polypeptides and compositions have utilities in toxicology testing and drug discovery regardless of knowing the biological function of the claimed polypeptides, and that these utilities would have been understood by one of skill in the art who read the Hillman '402 application on or before May 13, 1998. In particular, how the claimed polypeptides can be used in protein expression analysis techniques such as ***2-D PAGE technologies and western blots*** in connection with the development of drugs and the monitoring of the activity and the potential toxic effect of such drug candidates. (Furness Declaration at, e.g., ¶¶ 11-14).

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. (Furness Declaration at ¶ 11.)

Much, but not all, of Mr. Furness' explanation concerns the use of the claimed polypeptides in the creation of protein expression maps using 2-D PAGE. The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing.

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, Tab C, page 26).

Thus, the use of the claimed invention in the well known molecular biology techniques of ***2-D PAGE gels and western blots*** used to determine expression and toxicity of SEQ ID NO:3 and SEQ ID NO:5 are ***well established*** utilities and asserted in the Specification. The Furness Declaration provides objective evidence that a person of ordinary skill in the art can achieve beneficial results from the claimed polypeptides in the absence of any knowledge as to the precise function of the proteins. Further, the uses of the claimed polypeptides for protein expression monitoring applications including toxicology testing are in fact independent of its precise function. Additionally, one of ordinary skill in the art would regard toxicity testing, disease diagnosis and drug testing as ***well known*** utilities for the claimed invention.

Therefore, Applicants have enabled one reasonably skilled in the art to use the claimed invention without undue experimentation as evidenced by the disclosure in the Specification, the corroborating evidence of the Furness Declaration and through techniques in molecular biology which are both well established and ***well known*** to the reasonably skilled artisan.

D. The Specification Provides an Enabling Disclosure Commensurate with the Scope of the Claimed Invention

Applicants' amendment to claim 21 was faxed to the Examiner on April 7, 2003 in order to include recitation of a functional limitation for 90% variants of SEQ ID NO:3 and SEQ ID NO:5. Claim 21, by entry of the amendment now reads:

> 21. (Four Times Amended) An isolated polypeptide selected from the group consisting of:
>
> a) a polypeptide comprising the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5;
>
> b) a polypeptide comprising a naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, said polypeptide having apoptotic activity;
>
> c) a biologically-active fragment of at least 30 contiguous amino acid residues of a polypeptide having the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, said fragment having apoptotic activity; and
>
> d) an immunogenic fragment of at least 30 contiguous amino acid residues of a polypeptide having the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5.

The Examiner is well aware that the relative skill of those in the art is very high and the amount of direction or guidance needed to be disclosed in the Specification **to make** the proteins, variants and fragments of SEQ ID NO:3 and SEQ ID NO:5 as "now" claimed is well within the grasp of one of skill in the art upon reading the Specification. The Specification fully enables the making of the SEQ ID NO:3 and SEQ ID NO:5 polypeptides. (See, e.g., Sequence Listing and Specification, page 25, line 7 through page 30, line 28). Claimed variants, biologically active and immunogenic fragments of SEQ ID NO:3 or SEQ ID NO:5 are defined in the Specification at, for example, at page 21, lines 8-11, page 9, lines 18-27, page 10, line 29 to page 11, line 3, and page 17, line 24 to page 18, line 2. The Examiner stated that "[t]he disclosure does not provide any information disclosing what fragments of SEQ ID NO:3 or SEQ ID NO:5 should be regarded as biologically active or immunogenic or what sequences in the native amino acid sequences can be mutated/changed to yield a 90% variant with apoptotic activity." (Office Action mailed June 17, 2003, page 4). Polypeptide sequence variants are known by one of skill in the art to have amino acid substitutions which do not alter the function of the

polypeptide. For example, a change of an amino acid residue to another at the extreme amino- or the carboxy-terminus of the sequence most likely will not alter the function of the polypeptide. The Specification defines specific structural domains related to HAPOP-2 and HAPOP-3 proteins at page 19, lines 4-15 and page 19, line 28 to page 20, line 10.

Additionally, the Specification teaches methods to determine expression and/or activity of 90% variants and fragments of SEQ ID NO:3 or SEQ ID NO:5 having apoptotic activity include (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS) assays, as well as an HAPOP expression assay. (See for example, Specification, page 29, lines 17-20, and pages 58-59, Example X). Assays to determine functional activity are considered routine experimentation when identifying functional sequence variants and fragments. One of ordinary skill in the art would recognize the polypeptide sequences of SEQ ID NO:3 and SEQ ID NO:5 as well as the recited "90% variants of the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, said polypeptide having apoptotic activity," and fragments of SEQ ID NO:3 or SEQ ID NO:5, as those polypeptides or fragments which, when assayed, have at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5. Accordingly, polypeptides comprising an amino acid sequence that is 90% identical to the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5 or biologically active or immunogenic fragments of SEQ ID NO:3 or SEQ ID NO:5 can easily be identified by one of skill in the art based on both the presence of functional and structural domains and by the assay, all disclosed in the Specification.

Similarly, immunogenic fragments of the claimed polypeptides are described in the Specification in such as way as to enable one skilled in the relevant art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Specification, at page 9, lines 20-23, teaches that the immunogenic fragments of HAPOP are preferably about 5 to about 15 amino acids in length. Moreover, at pages 59-60, Example XII, the Specification specifically teaches how to use the claimed immunogenic fragments to produce HAPOP specific antibodies.

Likewise, the Specification, in Example XII (Specification page 59, line 22 to page 60, line 9) teaches both a method of making antibodies specific to SEQ ID NO:3 or SEQ ID NO:5, but also, how to identify immunogenic fragments within SEQ ID NO:3 or SEQ ID NO:5 using techniques and computer software programs well established and ***well known*** to the reasonably skilled artisan for

many years prior to the filing of the parent application, May 13, 1998. Thus, the skilled artisan is enabled, both by the teachings in the Specification *supra*, and by what was well known in the art to the ordinary artisan for many years prior to the filing of the part application how to make the immunogenic fragments of SEQ ID NO:3 and SEQ ID NO:5.

Note that Claim 21 recites not only that the variant polypeptides have at least 90% sequence identity to SEQ ID NO:3 or SEQ ID NO:5, but also have "***a naturally-occurring amino acid sequence***" and have "apoptotic activity." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:3 and SEQ ID NO:5, and SEQ ID NO:4 and SEQ ID NO:6 (the polynucleotide sequences encoding HAPOP-2 and HAPOP-3, respectively), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, said polypeptide having apoptotic activity." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. See, *e.g.*, page 16, line 1 to page 17, line 7; page 42, line 20 to page 43, line 2; and Example VI at pages 55-56.

Thus, one skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature. By adjusting the nature of the probe or nucleic acid (i.e., non-conserved, conserved or highly conserved) and the conditions of hybridization (maximum, high, intermediate or low stringency), one can obtain variant polynucleotides of SEQ ID NO:4 or SEQ ID NO:6 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:3 or SEQ ID NO:5 recited by the present claims. Conventional methods for making polypeptides and fragments thereof, such as those described at page 25, lines 7-16 and page 31, lines 23-28 of the Specification, could then be used to make the recited polypeptide variants.

E. Evidence of Domains Conserved Within Apoptosis Inducing Proteins Further Enable Determination of Those 90% Variants, Biologically Active and Immunogenic Fragments of SEQ ID NO:3 and SEQ ID NO:5

Applicants bring to the Examiner's attention the presence of structurally conserved domains within SEQ ID NO:3 and SEQ ID NO:5 that are found in proteins having apoptotic activity. Conserved domains within SEQ ID NO:3 are identified in the Specification at page 19, lines 4-15 and within SEQ ID NO:5 at page 19, line 28 to page 20, line 10. Since claim 21 was amended to include the function of 'having apoptotic activity,' Applicants and one of ordinary skill in the art would know that the presence of such domains within SEQ ID NO:3 and SEQ ID NO:5 are also structural properties of the claimed 90% variants, and biologically and immunologically active fragments of a polypeptide having the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present Specification combined with what is ***well known*** by one of ordinary skill in the art would *not* enable one to make and use the polypeptides of SEQ ID NO:3 or SEQ ID NO:5 as well as the recited "90% variants of the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, said polypeptide having apoptotic activity," "biologically-active fragments of a polypeptide having the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, said fragment having apoptotic activity" and "immunogenic fragments of SEQ ID NO:3 or SEQ ID NO:5" (the amino acid sequences of HAPOP-2 and HAPOP-3, respectively). Hence, a *prima facie* case for non-enablement has not been established with respect to the polypeptides of SEQ ID NO:3 or SEQ ID NO:5 as well as the recited "variants," "biologically-active fragments" and immunogenic fragments of SEQ ID NO:3 or SEQ ID NO:5.

F. By Requiring the Patent Applicants to Assert Corollary Evidence in Support of Either *In vito* or *In vivo* Data in Support of the Claimed Inventions for Use in Toxicological Screening, Disease Diagnosis or Drug Discovery, the Patent Examiner Has Misapplied the Enablement Guidelines

There is an additional, independent reason to reverse the enablement rejection. To the extent the rejections are based on *In re Wands* (858 F.2d at 737, 8 USPQ2d at 1404), the Examiner has failed to evaluate how to make and use the claimed inventions.

The Test of Enablement, requires that the Specification provide an enabling disclosure such that "any person skilled in the art can make and use the invention without undue experimentation" (M.P.E.P. § 2164.01 and *In re Wands* (858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)). The invention that one of ordinary skill in the art must be enabled to make and use is that defined by the claim(s) of the particular application or patent. The M.P.E.P. states that:

> [a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). (M.P.E.P. § 2164.01(b))
>
> [i]f a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U. S.C. 112 is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). See also *In re Brana*, 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993). (M.P.E.P. § 2164.01(c))
>
> When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). (M.P.E.P. § 2164.01(c))

The M.P.E.P. directs that when assessing if a particular claim is enabled, the making and using of the claimed invention is evaluated based on the Specification disclosing at least one method for making and using the claimed invention within a reasonable correlation of the scope of the claim. Further, when, as in the instant application, the claimed composition is limited by a particular use, i.e., having apoptosis activity, enablement should be evaluated based on said use.

As described *supra*, the Specification at the time of filing together with what is well known in the art, provides an enabling disclosure such that one of ordinary skill in the art can make and use SEQ ID NO:3 and SEQ ID NO:5 as well as determine those polypeptide sequence variants and fragments of SEQ ID NO:3 and SEQ ID NO:5 which have apoptotic activity. No further requirements to fulfill the enablement requirement is needed.

Further, Applicants respectfully submit that the Examiner has already determined that the claimed polypeptides have specific, substantial and credible utilities under 35 U.S.C. § 101 and 112. These utilities include using the claimed polypeptides in such applications as toxicity testing and protein

expression monitoring as Applicants argued in their Response filed March 19, 2001. Such uses are well known to the skilled artisan and do not have to be disclosed in the Specification. Thus, rejections for lack of enablement, based *inter alia*, on an allegation of "lack of corollary evidence," as set forth in the Office Action of November 4, 2002 and as justified in as not being within the scope of the Forman factors, alleging that Applicants have not "provided any objective evidence (neither *in vitro* nor *in vivo*) or data that supports the use of SEQ ID NO:3 and 5, also known [as] HAPOP for toxicological screening, disease diagnosis or drug discovery," are not supported by the prosecution history (Office Action of November 4, 2002, pages 3-4). The Specification discloses and one of ordinary skill in the art would understand that the claimed polypeptides are enabled within the scope of the claims.

G. Conclusion

Applicants have provide enablement commensurate with the scope of the claimed invention such that the reasonably skilled artisan is enabled to make and use the claimed invention in protein expression monitoring applications including toxicology testing, drug development and disease diagnosis. Thus, Applicants' have enabled one reasonably skilled in the art to be able to make and use the claimed invention without undue experimentation as evidenced by the disclosure in the Specification, the corroborating evidence of the Furness Declaration and through techniques and sequence analysis tools in molecular biology which are both well established and ***well known*** to the reasonably skilled artisan.

Accordingly, for all the above reasons, the claimed polypeptides of SEQ ID NO:3 and SEQ ID NO:5 as well as the recited naturally-occurring 90% variants of "the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, said polypeptide having apoptotic activity," biologically-active fragments "of a polypeptide having the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, said fragment having apoptotic activity" and immunogenic fragments of SEQ ID NO:3 or SEQ ID NO:5 (the amino acid sequences of HAPOP-2 and HAPOP-3, respectively) are enabled within the scope of the claimed invention. Therefore, for all the above reasons, Applicants respectfully requests reconsideration and withdrawal of the rejection of claims 21, 27, 28 and 43-45 for lack of scope of enablement under 35 U.S.C. 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph, written description

Claims 21, 22, 27, 28 and 43-45 were rejected under 35 U.S.C. §112, first paragraph, allegedly because the Specification contained "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." The Office Action asserts that:

- the written description is not commensurate in scope with the claims drawn to naturally-occurring amino acid sequences sharing 90% sequence identity. (Office Action of June 17, 2003, page 5);

- the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Lts.*, 18 USPQ 2d 1016. (Office Action of June 17, 2003, page 5);

- There is no disclosure, suggesting Applicants were in possession of sequence variants sharing 90% sequence identity with either SEQ ID NO:3 or SEQ ID NO:5. (Office Action of June 17, 2003, page 6).

This rejection is respectfully traversed.

At the outset, note that this rejection should not apply to claims 22, 28 and 43, because the recited "variants" of SEQ ID NO:3 and SEQ ID NO:5 are not within the scope of claims 22, 28 and 43.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

> . . . Mention of representative compounds encompassed by generic claim language ***clearly is not required by Section 112 or any other provision of the statute***. But, where no explicit description of a generic invention is to be found in the specification...mention of representative compounds may provide an implicit description upon which to base generic claim language. *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) [emphasis added]

> . . . [I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, ***it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.'*** *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960) [emphasis added]

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., ***complete or partial structure***, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. ***If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.*** [footnotes omitted, emphasis added]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The Specification Provides an Adequate Written Description of the Claimed "Variants" of SEQ ID NO:3 and SEQ ID NO:5

The subject matter encompassed by claims 21, 22, 27, 28 and 43-45 is either disclosed by the Specification or conventional or well known to one skilled in the art.

Independent claim 21 b) recites a polypeptide that is 1) "a naturally occurring amino acid sequence" that is 2) "at least 90% identical to the amino acid sequence of SEQ ID NO:3 or SEQ ID

NO:5" and having 3) "apoptotic activity." The Examiner's position is based upon the theory that the "written description in this instant case only sets forth SEQ ID NO:3 and SEQ ID NO:5 consisting of 238 and 410 amino acids, respectively therefore the written description is not commensurate in scope with the claims drawn to naturally-occurring amino acid sequences sharing 90% sequence identity (Office Action of June 17, 2003 at pages 4- 5). Applicants strongly disagree with this position.

Such a position ignores that the polypeptides recited in claim 21 b) ***are*** described in terms of their structure. That is, the claimed polypeptides are "***at least 90% identical to the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:***5." The structure of SEQ ID NO:3 and SEQ ID NO:5 is provided in the Specification, for example, at pages 64-66 of the Sequence Listing and Figures 1A and 1B for SEQ ID NO:3 and Figures 2A and 2B for SEQ ID NO:5. Definitions of the phrases "percent identity" or "% identity" as well as methods for determining such identity are provided, for example, at page 13, lines 2-18. A definition of polypeptide "variants," the types of amino acid changes and substitutions that may be made while still retaining biological or immunological activity, and computer programs well known in the art which provide guidance in identifying such variants may be found, for example, on page 17, line 24 to page 18, line 2. A detailed description of the chemical and structural features of SEQ ID NO:3 and SEQ ID NO:5 which contribute to the characterization of SEQ ID NO:3 or SEQ ID NO:5 and other related proteins as apoptosis associated proteins, including a description of which amino acid residues must be conserved to retain apoptotic activity are provided, for example, at page 19, lines 3-13 and page 19, line 27 to page 20, line 8. Ninety percent variants of the claimed polypeptides are described, for example, at page 21, lines 8-11.

Furthermore, claim 21, for example, recites not only that the polypeptide "variants" have apoptotic activity as well as having at least 90% sequence identity to SEQ ID NO:3 or SEQ ID NO:5, but also have "***a naturally-occurring amino acid sequence***." Through the process of natural selection, nature will have determined the appropriate polypeptide sequences. Given the information provided by SEQ ID NO:3 or SEQ ID NO:5 (the amino acid sequence of HAPOP-2 or HAPOP-3, respectively) and SEQ ID NO:4 or SEQ ID NO:6 (the polynucleotide sequence encoding HAPOP-2 or HAPOP-3, respectively), one of skill in the art would be able to routinely obtain "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, said naturally occurring amino acid sequence having apoptotic activity" as recited in

claim 21. For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. See, *e.g.*, page 42, lines 20-27 and Example VI at pages 55-56. Thus, one skilled in the art need not make and test vast numbers of polynucleotide sequences that are based on the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature. Moreover, once a candidate polypeptide is identified, its activity can be tested, *e.g.*, using an assay such as that which is set forth in Example X on pages 58-59.

When provided with the detailed description as noted above, one of ordinary skill in the art "would have understood the inventor to be in possession of the claimed invention at the time of filing." That is, one of ordinary skill in the art would recognize polypeptide sequence variants which are at least 90% identical to SEQ ID NO:3 or SEQ ID NO:5. Given any naturally occurring polypeptide sequence having apoptotic activity, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:3 or SEQ ID NO:5 and to determine the % identity to SEQ ID NO:3 or SEQ ID NO:5 of the variant. Accordingly, the Specification provides an adequate written description of the recited variants of SEQ ID NO:3 or SEQ ID NO:5.

B. The Specification Provides an Adequate Written Description as Required by Law

Applicants submit that caselaw in the area of the written description requirement of 35 U.S.C. 112, first paragraph is clear with regard to the details considered sufficient to describe a claimed genus:

> . . . Mention of representative compounds encompassed by generic claim language ***clearly is not required by Section 112 or any other provision of the statute***. But, where no explicit description of a generic invention is to be found in the specification . . . mention of representative compounds may provide an implicit description upon which to base generic claim language. *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) [emphasis added]

> . . . [I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, ***it may not be necessary to enumerate a plurality of species if a genus is sufficiently***

> ***identified in an application by 'other appropriate language.'*** *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960) [emphasis added]

The Specification sets forth a description of the claimed polypeptide variants using "other appropriate language" as indicated above in connection with the remarks regarding "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, said naturally occurring amino acid sequence having apoptotic activity." The claimed variants have been described in terms of their relationship to the chemical structure of SEQ ID NO:3 or SEQ ID NO:5 and structural requirements for biological and immunological activity at, for example, pages 64-66 of the Sequence Listing; Figures 1A and 1B for SEQ ID NO:3 and Figures 2A and 2B for SEQ ID NO:5; page 19, lines 3-19; page 19, line 27 to page 20, line 14. The Specification provides a means of identifying naturally occurring functional variants having 90% sequence identity with SEQ ID NO:3 or SEQ ID NO:5 and having apoptotic activity at, for example, page 17, line 24 to page 18, line 2; page 42, lines 20-27; Example VI at pages 55-56; and Example X at pages 58-59. Applicants therefore submit that the "genus is sufficiently identified in [the instant] application by 'other appropriate language'" as stated in *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960). Furthermore, Applicants submit that "a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing" as stated in the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001. Accordingly, claims 21, 22, 27, 28 and 43-45 meet the statutory requirements for written description under 35 U.S.C. 112, first paragraph.

C. Conclusion

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims in view of their scope. In particular, the subject matter of the claims of the instant application is defined in terms of the chemical structure of SEQ ID NO:3 and SEQ ID NO:5. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides defined by the present claims is adequately described,

as evidenced by specific passages of the Specification as set forth above. Furthermore, the Examiner has applied to the subject application a written description standard that has no basis in the law.

For at least the above reasons it is believed that claims 21, 22, 27, 28 and 43-45 meet the written description requirement of 35 U.S.C. § 112, first paragraph. It is therefore requested that this rejection be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicant's Agent at (650) 621-8555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,
INCYTE CORPORATION

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